Patent Claims for USA: 92/B 024 - Ma 957

1. A compound containing an antigen binding region which is bound to at least one prodrug-activating enzyme, where the antigen binding region is composed of a single polypeptide chain.

2. A compound as claimed in claim 1, wherein the compound carries covalently bonded carbohydrates.

3. A compound as claimed in claim 1, wherein the antigen binding region contains a variable domain of a heavy antibody chain and a variable domain of a light antibody chain (sFv fragment).

4. A compound as claimed in claim 1, wherein the antigen binding region binds to a tumor-associated antigen (TAA).

5. A compound as claimed in claim 3, wherein the TAA is an N-CAM, PEM, EGF-R, Sialyl-Le^a, Sialyl-Le^x, TFß, GICA, GD_3, GD_2, TAG72, CA125, the 24-25 kDa glycoprotein defined by MAb L6, or CEA, preferably a CEA.

6. A compound as claimed in claim 1, wherein the enzyme is a lactamase, preferably a Bacillus cereus II ß-lactamase, pyroglutamate aminopeptidase, D-aminopeptidase, oxidase, peroxidase, phosphatase, hydroxynitrile lyase, protease, esterase, carboxypeptidase, preferably a carboxypeptidase G2 from Pseudomonas or glycosidase.

7. A compound as claimed in claim 6, wherein the enzyme is a ß-glucuronidase, preferably a E.coli, Kobayasia nipponica, Secale cereale or human ß-glucuronidase.

8. A compound as claimed in claim 1, wherein the antigen binding region is linked to the enzyme via a peptide linker.

9. A compound as claimed in claim 1, wherein the glycosylation takes place either by means of chemical methods or by a selection of suitable expression systems.

10. A compound as claimed in claim 1, which undergoes secretory expression in Saccharomyces cerevisiae or, more advantageously, in Hansenula polymorpha.

11. A compound as claimed in claim 1, which is expressed in E. coli and is subsequently chemically glycosylated, preferably galactosylated and/or mannosylated.

12. A compound as claimed in claim 1, wherein the sFv-ß-lactamase fusion protein, which has undergone periplasmic expression in E. coli, is chemically glycosylated, preferably galactosylated and/or mannosylated.

13. A compound as claimed in claim 1, wherein the sFv-ß-lactamase fusion protein undergoes secretory expression in Saccharomyces cerevisiae or Hansenula polymorpha.

14. A nucleic acid coding for a compound as claimed in claim 1.

15. A nucleic acid as claimed in claim 14, coding for a humanized sFv fragment against CEA and a human β-glucuronidase.

16. A nucleic acid as claimed in claim 14 with the sequence

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CCAAGCTTAT GAATATGCAA ATCCTGCTCA TGAATATGCA AATCCTCTGA                  50

ATCTACATGG TAAATATAGG TTTGTCTATA CCACAAACAG AAAAACATGA                 100

GATCACAGTT CTCTCTACAG TTACTGAGCA CACAGGACCT CACC ATG GGA TGG           153
                                                 Met Gly Trp

AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGTAAGGGGC             199
Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr
                        -10
TCACAGTAGC AGGCTTGAGG TCTGGACATA TATATGGGTG ACAATGACAT                 249

CCACTTTGCC TTTCTCTCCA CA GGT GTC CAC TCC CAG GTC CAA CTG CAG           298
                         Gly Val His Ser Gln Val Gln Leu Gln
                                                1
GAG AGC GGT CCA GGT CTT GTG AGA CCT AGC CAG ACC CTG AGC CTG            343
Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln Thr Leu Ser Leu
                   10                                  20
ACC TGC ACC GTG TCT GGC TTC ACC ATC AGC AGT GGT TAT AGC TGG            388
Thr Cys Thr Val Ser Gly Phe Thr Ile Ser Ser Gly Tyr Ser Trp
                                    30
CAC TGG GTG AGA CAG CCA CCT GGA CGA GGT CTT GAG TGG ATT GGA            433
His Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile Gly
                   40                                  50
TAC ATA CAG TAC AGT GGT ATC ACT AAC TAC AAC CCC TCT CTC AAA            478
Tyr Ile Gln Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys
                                    60
AGT AGA GTG ACA ATG CTG GTA GAC ACC AGC AAG AAC CAG TTC AGC            523
Ser Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln Phe Ser
                   70                                  80
CTG AGA CTC AGC AGC GTG ACA GCC GCC GAC ACC GCG GTC TAT TAT            568
Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                                    90
TGT GCA AGA GAA GAC TAT GAT TAC CAC TGG TAC TTC GAT GTC TGG            613
Cys Ala Arg Glu Asp Tyr Asp Tyr His Trp Tyr Phe Asp Val Trp
                  100                                 110
GGC CAA GGG ACC ACG GTC ACC GTC TCC TCA GGA GGC GGT GGA TCG            658
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser
                                   120
GGC GGT GGT GGG TCG GGT GGC GGC GGA TCT GAC ATC CAG CTG ACC            703
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr
                  130                                 140
CAG AGC CCA AGC AGC CTG AGC GCC AGC GTG GGT GAC AGA GTG ACC            748
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                                   150
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ATC ACC TGT AGT ACC AGC TCG AGT GTA AGT TAC ATG CAC TGG TAC  793
Ile Thr Cys Ser Thr Ser Ser Ser Val Ser Tyr Met His Trp Tyr
                 160                                 170
CAG CAG AAG CCA GGT AAG GCT CCA AAG CTG CTG ATC TAC AGC ACA  838
Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Thr
                                 180
TCC AAC CTG GCT TCT GGT GTG CCA AGC AGA TTC AGC GGT AGC GGT  883
Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
                 190                                 200
AGC GGT ACC GAC TTC ACC TTC ACC ATC AGC AGC CTC CAG CCA GAG  928
Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
                                 210
GAC ATC GCC ACC TAC TAC TGC CAT CAG TGG AGT AGT TAT CCC ACG  973
Asp Ile Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Tyr Pro Thr
                 220                                 230
TTC GGC CAA GGG ACC AAG CTG GAG ATC AAA GGTGAGTAGA ATTTAAACTT 1023
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                                 240
TGCTTCCTCA GTTGGATCTG AGTAACTCCC AATCTTCTCT CTGCA GAG CTC AAA 1077
                                                Glu Leu Lys
ACC CCA CTT GGT GAC ACA ACT CAC ACA TGC CCA CGG TGC CCA       1119
Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys Pro
                         250
GGTAAGCCAG CCCAGGACTC GCCCTCCAGC TCAAGGCGGG ACAAGAGCCC       1169

TAGAGTGGCC TGAGTCCAGG GACAGGCCCC AGCAGGGTGC TGACGCATCC       1219

ACCTCCATCC CAGATCCCCG TAACTCCCAA TCTTCTCTCT GCA GCG GCG GCG  1271
                                            Ala Ala Ala
                                                        260
GCG GTG CAG GGC GGG ATG CTG TAC CCC CAG GAG AGC CCG TCG CGG  1316
Ala Val Gln Gly Gly Met Leu Tyr Pro Gln Glu Ser Pro Ser Arg
                                 270
GAG TGC AAG GAG CTG GAC GGC CTC TGG AGC TTC CGC GCC GAC TTC  1361
Glu Cys Lys Glu Leu Asp Gly Leu Trp Ser Phe Arg Ala Asp Phe
                 280                                 290
TCT GAC AAC CGA CGC CGG GGC TTC GAG GAG CAG TGG TAC CGG CGG  1406
Ser Asp Asn Arg Arg Arg Gly Phe Glu Glu Gln Trp Tyr Arg Arg
                                 300
CCG CTG TGG GAG TCA GGC CCC ACC GTG GAC ATG CCA GTT CCC TCC  1451
Pro Leu Trp Glu Ser Gly Pro Thr Val Asp Met Pro Val Pro Ser
                 310                                 320
AGC TTC AAT GAC ATC AGC CAG GAC TGG CGT CTG CGG CAT TTT GTC  1496
Ser Phe Asn Asp Ile Ser Gln Asp Trp Arg Leu Arg His Phe Val
                                 330
GGC TGG GTG TGG TAC GAA CGG GAG GTG ATC CTG CCG GAG CGA TGG  1541
Gly Trp Val Trp Tyr Glu Arg Glu Val Ile Leu Pro Glu Arg Trp
                 340                                 350
ACC CAG GAC CTG CGC ACA AGA GTG GTG CTG AGG ATT GGC AGT GCC  1586
Thr Gln Asp Leu Arg Thr Arg Val Val Leu Arg Ile Gly Ser Ala
                                 360
CAT TCC TAT GCC ATC GTG TGG GTG AAT GGG GTC GAC ACG CTA GAG  1631
His Ser Tyr Ala Ile Val Trp Val Asn Gly Val Asp Thr Leu Glu
                 370                                 380
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CAT GAG GGG GGC TAC CTC CCC TTC GAG GCC GAC ATC AGC AAC CTG    1676
His Glu Gly Gly Tyr Leu Pro Phe Glu Ala Asp Ile Ser Asn Leu
                                    390
GTC CAG GTG GGG CCC CTG CCC TCC CGG CTC CGA ATC ACT ATC GCC    1721
Val Gln Val Gly Pro Leu Pro Ser Arg Leu Arg Ile Thr Ile Ala
                400                                 410
ATC AAC AAC ACA CTC ACC CCC ACC ACC CTG CCA CCA GGG ACC ATC    1766
Ile Asn Asn Thr Leu Thr Pro Thr Thr Leu Pro Pro Gly Thr Ile
                                    420
CAA TAC CTG ACT GAC ACC TCC AAG TAT CCC AAG GGT TAC TTT GTC    1811
Gln Tyr Leu Thr Asp Thr Ser Lys Tyr Pro Lys Gly Tyr Phe Val
                430                                 440
CAG AAC ACA TAT TTT GAC TTT TTC AAC TAC GCT GGA CTG CAG CGG    1856
Gln Asn Thr Tyr Phe Asp Phe Phe Asn Tyr Ala Gly Leu Gln Arg
                                    450
TCT GTA CTT CTG TAC ACG ACA CCC ACC ACC TAC ATC GAT GAC ATC    1901
Ser Val Leu Leu Tyr Thr Thr Pro Thr Thr Tyr Ile Asp Asp Ile
                460                                 470
ACC GTC ACC ACC AGC GTG GAG CAA GAC AGT GGG CTG GTG AAT TAC    1946
Thr Val Thr Thr Ser Val Glu Gln Asp Ser Gly Leu Val Asn Tyr
                                    480
CAG ATC TCT GTC AAG GGC AGT AAC CTG TTC AAG TTG GAA GTG CGT    1991
Gln Ile Ser Val Lys Gly Ser Asn Leu Phe Lys Leu Glu Val Arg
                490                                 500
CTT TTG GAT GCA GAA AAC AAA GTC GTG GCG AAT GGG ACT GGG ACC    2036
Leu Leu Asp Ala Glu Asn Lys Val Val Ala Asn Gly Thr Gly Thr
                                    510
CAG GGC CAA CTT AAG GTG CCA GGT GTC AGC CTC TGG TGG CCG TAC    2081
Gln Gly Gln Leu Lys Val Pro Gly Val Ser Leu Trp Trp Pro Tyr
                520                                 530
CTG ATG CAC GAA CGC CCT GCC TAT CTG TAT TCA TTG GAG GTG CAG    2126
Leu Met His Glu Arg Pro Ala Tyr Leu Tyr Ser Leu Glu Val Gln
                                    540
CTG ACT GCA CAG ACG TCA CTG GGG CCT GTG TCT GAC TTC TAC ACA    2171
Leu Thr Ala Gln Thr Ser Leu Gly Pro Val Ser Asp Phe Tyr Thr
                550                                 560
CTC CCT GTG GGG ATC CGC ACT GTG GCT GTC ACC AAG AGC CAG TTC    2216
Leu Pro Val Gly Ile Arg Thr Val Ala Val Thr Lys Ser Gln Phe
                                    570
CTC ATC AAT GGG AAA CCT TTC TAT TTC CAC GGT GTC AAC AAG CAT    2261
Leu Ile Asn Gly Lys Pro Phe Tyr Phe His Gly Val Asn Lys His
                580                                 590
GAG GAT GCG GAC ATC CGA GGG AAG GGC TTC GAC TGG CCG CTG CTG    2306
Glu Asp Ala Asp Ile Arg Gly Lys Gly Phe Asp Trp Pro Leu Leu
                                    600
GTG AAG GAC TTC AAC CTG CTT CGC TGG CTT GGT GCC AAC GCT TTC    2351
Val Lys Asp Phe Asn Leu Leu Arg Trp Leu Gly Ala Asn Ala Phe
                610                                 620
CGT ACC AGC CAC TAC CCC TAT GCA GAG GAA GTG ATG CAG ATG TGT    2396
Arg Thr Ser His Tyr Pro Tyr Ala Glu Glu Val Met Gln Met Cys
                                    630
GAC CGC TAT GGG ATT GTG GTC ATC GAT GAG TGT CCC GGC GTG GGC    2441
Asp Arg Tyr Gly Ile Val Val Ile Asp Glu Cys Pro Gly Val Gly
                640                                 650
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CTG GCG CTG CCG CAG TTC TTC AAC AAC GTT TCT CTG CAT CAC CAC      2486
Leu Ala Leu Pro Gln Phe Phe Asn Asn Val Ser Leu His His His
                                660
ATG CAG GTG ATG GAA GAA GTG GTG CGT AGG GAC AAG AAC CAC CCC      2531
Met Gln Val Met Glu Glu Val Val Arg Arg Asp Lys Asn His Pro
            670                                         680
GCG GTC GTG ATG TGG TCT GTG GCC AAC GAG CCT GCG TCC CAC CTA      2576
Ala Val Val Met Trp Ser Val Ala Asn Glu Pro Ala Ser His Leu
                                690
GAA TCT GCT GGC TAC TAC TTG AAG ATG GTG ATC GCT CAC ACC AAA      2621
Glu Ser Ala Gly Tyr Tyr Leu Lys Met Val Ile Ala His Thr Lys
            700                                         710
TCC TTG GAC CCC TCC CGG CCT GTG ACC TTT GTG AGC AAC TCT AAC      2666
Ser Leu Asp Pro Ser Arg Pro Val Thr Phe Val Ser Asn Ser Asn
                                720
TAT GCA GCA GAC AAG GGG GCT CCG TAT GTG GAT GTG ATC TGT TTG      2711
Tyr Ala Ala Asp Lys Gly Ala Pro Tyr Val Asp Val Ile Cys Leu
            730                                         740
AAC AGC TAC TAC TCT TGG TAT CAC GAC TAC GGG CAC CTG GAG TTG      2756
Asn Ser Tyr Tyr Ser Trp Tyr His Asp Tyr Gly His Leu Glu Leu
                                750
ATT CAG CTG CAG CTG GCC ACC CAG TTT GAG AAC TGG TAT AAG AAG      2801
Ile Gln Leu Gln Leu Ala Thr Gln Phe Glu Asn Trp Tyr Lys Lys
            760                                         770
TAT CAG AAG CCC ATT ATT CAG AGC GAG TAT GGA GCA GAA ACG ATT      2846
Tyr Gln Lys Pro Ile Ile Gln Ser Glu Tyr Gly Ala Glu Thr Ile
                                780
GCA GGG TTT CAC CAG GAT CCA CCT CTG ATG TTC ACT GAA GAG TAC      2891
Ala Gly Phe His Gln Asp Pro Pro Leu Met Phe Thr Glu Glu Tyr
            790                                         800
CAG AAA AGT CTG CTA GAG CAG TAC CAT CTG GGT CTG GAT CAA AAA      2936
Gln Lys Ser Leu Leu Glu Gln Tyr His Leu Gly Leu Asp Gln Lys
                                810
CGC AGA AAA TAT GTG GTT GGA GAG CTC ATT TGG AAT TTT GCC GAT      2981
Arg Arg Lys Tyr Val Val Gly Glu Leu Ile Trp Asn Phe Ala Asp
            820                                         830
TTC ATG ACT GAA CAG TCA CCG ACG AGA GTG CTG GGG ATT AAA AAG      3026
Phe Met Thr Glu Gln Ser Pro Thr Arg Val Leu Gly Asn Lys Lys
                                840
GGG ATC TTC ACT CGG CAG AGA CAA CCA AAA AGT GCA GCG TTC CTT      3071
Gly Ile Phe Thr Arg Gln Arg Gln Pro Lys Ser Ala Ala Phe Leu
            850                                         860
TTG CGA GAG AGA TAC TGG AAG ATT GCC AAT GAA ACC AGG TAT CCC      3116
Leu Arg Glu Arg Tyr Trp Lys Ile Ala Asn Glu Thr Arg Tyr Pro
                                870
CAC TCA GTA GCC AAG TCA CAA TGT TTG GAA AAC AGC CCG TTT ACT      3161
His Ser Val Ala Lys Ser Gln Cys Leu Glu Asn Ser Pro Phe Thr
            880                                         890
TGA GCAAGACTGA TACCACCTGC GTGTCCCTTC CTCCCCGAGT CAGGGCGACT      3214
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TCCACAGCAG CAGAACAAGT GCCTCCTGGA CTGTTCACGG CAGACCAGAA          3264

CGTTTCTGGC CTGGGTTTTG TGGTCATCTA TTCTAGCAGG GAACACTAAA          3314
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17. A vector containing a nucleic acid as claimed in claim 14.

18. A host cell containing a nucleic acid as claimed in claim 14 or a vector as claimed in claim 17.

19. A host cell as claimed in claim 18, which is a BHK, CHO, COS, HeLa, insect, tobacco plant, yeast or E.coli cell.

20. A transgenic mammal with the exception of a human, containing a DNA as claimed in claim 14 or a vector as claimed in claim 17.

21. A process for preparing a compound as claimed in claim 1, which comprises

a) introducing a nucleic acid as claimed in claim 14 or a vector as claimed in claim 17 into a host cell,

b) cultivating the host cell, and

c) isolating the compound.

22. A process for preparing a compound as claimed in claim 1, which comprises

a) cultivating a host cell as claimed in claim 18, and

b) isolating the compound.

23. The use of the compound as claimed in claim 1 for the preparation of a pharmaceutical or of a diagnostic aid.

24. The use of the compound as claimed in claim 1 for the preparation of a pharmaceutical for the treatment of cancer.

25. A pharmaceutical containing a compound as claimed in claim 1.

26. A diagnostic aid containing a compound as claimed in claim 1.